REMARKS

Applicant acknowledges receipt of the Office Action mailed May 6, 2003.

The title of the Application and Claim 105 are both amended by this filing. The title of the Application is amended herein to reflect more appropriately the instantly claimed invention. Claim 105 has been amended to indicate that positive and negative results which reflect the presence or absence of an analyte polynucleotide relative to a pre-determined value are determined "without reference to the amount of pseudo target amplicon synthesized in the co-amplifying step." Support for this amendment can be found in the Specification, for example, on page 9 starting at line 25 and extending to page 10 at line 9; on page 13 at lines 21-25; on page 16 at lines 8-10; on page 16 at lines 15-17; on page 17 at lines 10-12; and on page 19 at lines 2-5. The word "present" in the co-amplifying step of Claim 105 has been amended to "produced" to clarify that the analyte amplicon which is described as a "product" in the preceding line is "produced in an amount that is dose-dependent...." Finally, the second recitation of "a positive result" which appears in the last step of Claim 105 has been amended to instead read, "said positive result..." to correct an oversight in the claim syntax.

Claims 105-106, 108-110 and 116 will remain pending following entry of this Response.

No new matter is being added by this Amendment.

The Rejection Under § 102(e)

Claims 105-106 and 116 have been rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,952,202 ("**Aoyagi**") which discloses co-amplification and detection of a target polynucleotide and an internal control polynucleotide ("ICP") in a real-time format. According

to the cited reference, the two amplicon species are synthesized using different primer sets and are detected using different self-reporting probes. The rejection cited Example 5 as instructing that signals representing the detection of target and internal control polynucleotides could be detected as a "Ct value" which represents a threshold value for determining the presence or absence of DNA in a test sample. Although the rejection refers to col. 36, lines 1-26 of the prior art citation, Applicant believes this reference is in error because the Aoyagi patent does not contain col. 36.

The instant claims do not embrace the method of **Aoyagi** because the instantly claimed method requires procedural limitations that are not described in the cited reference. The Examiner correctly pointed out that the pre-determined threshold Ct value of 40 indicates there is no detectable DNA in the sample, whereas Ct values *below* this threshold indicate the *presence* of target and control polynucleotides. In contrast, the instantly claimed invention goes opposite this approach by indicating a positive result (i.e., the *presence* of an analyte polynucleotide) when the amount of amplicon *equals or exceeds* a pre-determined value, and indicates a negative result (i.e., the *absence* of an analyte polynucleotide) when the amount of amplicon is *below* the pre-determined value. This feature of the invention is set forth in the final step of amended Claim 105, which recites:

> quantitatively detecting said analyte amplicon using a detection system calibrated to indicate ***a positive result*** upon detecting an amount of analyte amplicon arising from co-amplification of said amount of said pseudo target and an amount of analyte polynucleotide ***equal to or greater than said pre-determined value***, wherein said positive result indicates that said analyte polynucleotide is present in said test sample in an amount equal to or greater than said pre-determined value, wherein ***a negative result*** indicates that said analyte polynucleotide is present in said test sample in an amount ***less than said pre-determined value***, and wherein said positive result and said negative result are

> determined without reference to the amount of pseudo target amplicon synthesized in the co-amplifying step. [***Emphasis added***]

The instant claims do not embrace the method of **Aoyagi**, and so the disclosure of **Aoygai** cannot anticipate the claims. **Aoyagi** cannot anticipate the instantly claimed invention because the results obtained by practicing the method disclosed therein leads to an opposite conclusion regarding the presence or absence of an analyte polynucleotide in a test sample. Accordingly, withdrawal of the rejection of Claims 105-106 and 116 under 35 U.S.C. § 102(e) is appropriate.

The Rejections Under § 103

Aoyagi et al., and Jurriaans et al.

Claims 109 and 110 have been rejected under 35 U.S.C. § 103(a) as obvious over the disclosure of the **Aoyagi** patent in view of a scientific journal article by Jurriaans et al., ("**Jurriaans**"). The rejection essentially states that, because **Aoyagi** discloses methods of amplifying an internal control polynucleotide, and because **Jurriaans** describes determining the amounts of HIV-1 RNA and DNA in clinical samples by nucleic acid amplification in a method of monitoring disease progression, it would have been obvious to use the method of **Aoyagi** for the detection of HIV-1 nucleic acids in accordance with **Jurriaans**. According to the rejection, one of ordinary skill in the art would have been motivated to use real-time nucleic acid amplification with internal controls to result in a rapid and accurate assay.

The invention defined by Claims 109 and 110 cannot be considered obvious under § 103(a) because the method taught by the primary reference leads to a conclusion regarding the presence or absence of an analyte polynucleotide that is opposite the conclusion reached by the instantly claimed method for the reasons elaborated above in response to the rejection under §

102(e). **Aoygai** requires determining the PCR cycle number at which a positive signal is obtained in order to determine the presence or absence of a target DNA in a sample. **Aoyagi** particularly describes conducting a total of 40 PCR cycles (See Example 5, and Example 2 which is referenced therein). A positive signal observed prior to completion of the 40 PCR cycles (i.e., a cycle number *below* the threshold) indicates the *presence* of a target polynucleotide. Even if the method of **Aoygai** were applied to the HIV-1 target of **Jurriaans**, the invention of Claims 109 (specifies a viral analyte polynucleotide) and 110 (specifies a viral polynucleotide that is any of an HIV-1, HIV-2, HBV or HCV polynucleotide) still would not result for the reasons given. Accordingly, the prior art cannot render obvious the invention of Claims 109 and 110 and so withdrawal of the rejection under § 103(a) is appropriate.

van Gemen et al.

Claims 105-106, 108-110 and 116 have been rejected under 35 U.S.C. § 103(a) as obvious in light of the disclosure contained in a single journal article by van Gemen et al. ("**van Gemen**"). The rejection describes the reference as disclosing co-amplification of HIV-1 target RNA ("WT") and three distinguishable internal standards (Q_A, Q_B and Q_C). The different amplification products were detected using different amplicon-specific probes, and the amount of target RNA calculated from the ratio of the WT and Q_A, Q_B and Q_C signals. The rejection is based on the notion that a pseudo target can be any polynucleotide which is co-amplified with the target polynucleotide (see Office Action on page 3). By the reasoning set forth in the rejection, the internal standards of **van Gemen** would fall within the scope of the instantly recited pseudo targets. According to the method of **van Gemen**, quantitation of the HIV-1 target analyte absolutely depends on quantitation of the internal standard amplicons.

Claim 105 has been amended to specify that "positive" and "negative" results "are determined without reference to the amount of pseudo target amplicon synthesized in the co-

amplifying step." If the Q_A, Q_B and Q_C polynucleotide standards of **van Gemen** are construed as "pseudo targets" for the purpose of the rejection, and because **van Gemen** instructs quantitation of target polynucleotides by a method that absolutely requires calculating the ratio of the WT and Q_A, Q_B and Q_C signals, it would not have been obvious from the prior art how to quantify an analyte polynucleotide without also determining the extent of amplification of multiple "pseudo targets." In contrast with the approach of **van Gemen**, and in accordance with the language of Amended Claim 105, the instantly recited positive and negative results are determined "without reference to the amount of pseudo target amplicon synthesized in the co-amplifying step." The meaning of this phrase should be clear from the definition appearing in the instant Specification on page 9 starting at line 25.

Since it would not have been obvious from the prior art how to determine whether an analyte polynucleotide was present in a test sample in an amount greater or less than a pre-determined threshold value without referring to the amount of a standard amplicon synthesized in an amplification reaction, it follows that the invention defined by Amended Claim 105 would not have been obvious in view of the **van Gemen** reference. Since all of the claims depend directly or indirectly from Claim 105, the claims incorporate the limitations of nonobvious Claim 105 and so also are nonobvious. Accordingly, withdrawal of the rejection under § 103(a) in light of the **van Gemen** article is appropriate.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the telephone number shown below.

Respectfully submitted,

GEN-PROBE INCORPORATED

Dated: Aug 29, 2003

By: _____

Michael J. Gilly
Registration No. 42,579
Agent of Record
Gen-Probe Incorporated
10210 Genetic Center Drive
San Diego, CA 92121
(858) 410-8657

104-03.Amend.1.wpd
August 26, 2003